201-15083

HPV ROBUST SUMMARIES

FOR

DIMETHYL METHYLPHOSPHONATE

December 23, 2003

Submitted By:

DMMP Consortium, consisting of:

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1. Substance Information

CAS Number:	756-79-6
Chemical Name:	Dimethyl methylphosphonate
Structural Formula:	$C_3H_9O_3P$
Physical State:	Liquid
Purity:	98.0-99.8%
Synonyms:	DMMP Dimethyl methanephosphonate, Phosphonic acid, methyl dimethyl ester Methanephosphonic acid, dimethyl ester
Uses:	Flame retardant, hydraulic fluid, antifoam agent, plasticizer, textile conditioner, antistatic agent
Exposure Limits:	None

2. Physical – Chemical Properties

2.1 Boiling Point:

Identity:	Fyrol DMMP
Method:	OPPTS 730.7220
Year:	Not known
GLP:	No
Value:	180.0°C
Conclusion:	The boiling point of Fyrol DMMP is 180.0°C.
Reliability:	4
Reference:	1

2.2 Vapor Pressure:

Identity:	Fyrol DMMP
Method:	OPPTS 730:7950

Year:	2000
GLP:	No
Value:	0.34 mmHg @ 25°C
Conclusion:	The vapor pressure of Fyrol DMMP is 0.34 mmHg @ 25°C.
Reliability:	2
Reference:	2

2.3 Specific Gravity

Identity:	Fyrol DMMP
Method:	OPPTS 830.7300
Year:	Not known
GLP:	No
Value:	1.16 @ 25°C
Conclusion:	The specific gravity (relative density) of Fyrol DMMP is 1.16 @ 25°C.
Reliability:	4
Reference:	1

2.4 Water Solubility

Identity:	Fyrol DMMP Lot No. 0114E-1
Method:	OECD 105
Year:	2001
GLP:	No
Value:	Fully miscible with water
Conclusion:	DMMP was fully miscible with water, when tested by adding up to 98.4% DMMP to water.
Reliability:	2
Reference:	3

2.4 Octanol:water Partition Coefficient

Identity:	Dimethyl Methylphosphate
Method:	OPPTS 830.7570
Year:	1988
GLP:	No
Value:	-0.61
Conclusion:	The n-octanol:water partition coefficient (log Kow) was determined by high performance liquid chromatography to be -0.61.
Reliability:	2
Reference:	4

Identity: Fyrol DMMP Lot No. 0114E-1

Method:	OECD 107
Year:	2001
GLP:	No
Value:	-1.3
Conclusion:	The n-octanol:water partition coefficient (log Kow) was determined by high performance liquid chromatography to be -1.3.
Reliability:	2
Reference:	3

3. Environmental Fate

3.1 Biodegradation

Identity:	Fyrol DMMP, Batch No. 8114 S-10-1
Guideline:	OECD 209 Activated Sludge – Respiration Inhibition Test
Year:	1990
GLP:	Yes
Method:	Fyrol DMMP was added to activated sludge containing synthetic sewage, at concentrations of 0, 1, 10, 100, 1000, and 10,000 mg/l, and incubated for 3 hours. 3,5-Dichlorophenol was used as the reference inhibitor.
Results:	The 3,5-dichlorophenol EC50 was 13.6 mg/l, confirming the test was valid. The respiration rate of the control culture did not change during the test. Fyrol DMMP at 1 and 10 g/l inhibited respiration by 20 and 31%, respectively, indicating the product does not substantially inhibit the respiration of activated sludge. The EC50 could not be calculated, but must be greater than 10 g/l.
Reliability:	1
Reference:	5

4. Ecotoxicity

4.1 Acute Toxicity to Fish

Identity:	Fyrol DMMP, Batch No. 8114 S-10-1
Guideline:	OECD 203 Acute Toxicity to Fish
Year:	1990
GLP:	Yes
Method:	Groups of rainbow trout were exposed to one of five nominal concentrations (560, 1000, 1800, 3200, and 5600 mg/l) of Fyrol DMMP. Ten fish per group were exposed for 96 hours. A control group was included in the study. Water conditions were: hardness202-216 mg/l as $CaCO_3$, pH 7.6-8.1, and temperature 13.2-14.9°C. Fish were observed at 0.25, 2, and 24 hours after start of exposure, and thereafter every 24 hours.
Results:	Mortality of 100% was observed in the 3200 and 5600 mg/l groups, while

there was no mortality in the 1000 mg/l group. The 96 hour median lethal concentration (LC50) was determined to be 2259 mg/l.

Reliability: 1
Reference: 6

5 Mammalian Toxicity

5.1 Acute Toxicity

5.11 Acute Oral Toxicity

Identity: Fyrol DMMP Lot No. 756-79-6
Guideline: 40 CFR 798.1175 Acute Oral Toxicity
Year: 1982
GLP: Yes
Method: Male and female Sprague-Dawley rats received a single 5000 mg/kg oral gavage dose of Fyrol DMMP, and were subsequently observed for signs of toxicity and for mortality. The animals were observed a minimum of once daily for the 14 day observation period.
Results: There were minimal signs of toxicity. The acute oral LD50 is > 5 g/kg.
Reliability: 1
Reference: 7

Identity: Dimethyl Methylphosphonate, Sample No. 540811
Guideline: Federal Hazardous Substances Act Regulations Part 1500
Year: 1981
GLP: Yes
Method: Male and female Sprague-Dawley rats received a single 5000 mg/kg oral gavage dose of dimethyl methylphosphonate and were subsequently observed for signs of toxicity and for mortality. The animals were observed once daily for the 14 day observation period.
Results: There were minimal signs of toxicity. The acute oral LD50 is > 5 g/kg.
Reliability: 1
Reference: 8

5.12 Acute Dermal Toxicity

Identity: Fyrol DMMP Lot No. 756-79-6
Guideline: U.S. EPA Guidelines for Registering Pesticides, Fed. Reg. 43:163, 37336
Year: 1982
GLP: Yes
Method: Four male and four female albino rabbits received a dermal application of 2000 mg/kg Fyrol DMMP to their abdominal skin, which was then

wrapped for 24 hours. The skin at the application site was abraded on half the animals. After 24 hours, the binding was removed.

Results: There was no mortality in this study. The acute dermal LD50 is > 2000 mg/kg.

Reliability: 1

Reference: 7

Identity: MCTR-196-77

Guideline: Not stated

Year: 1977

GLP: No

Method: Twelve male albino rabbits received a single dermal application of 5000 mg/kg of MCTR-196-77. The skin at the application site was abraded on half the animals. The animals were observed for mortality daily for 14 days.

Results: There was no mortality in this study. The acute dermal LD50 is > 5000 mg/kg.

Reliability: 2

Reference: 9

Identity: MCTR-129-78

Guideline: Not stated

Year: 1978

GLP: No

Method: Twelve male albino rabbits received a single dermal application of 5000 mg/kg of MCTR-129-78. The skin at the application site was abraded on half the animals. The animals were observed for mortality daily for 14 days.

Results: There was no mortality in this study. The acute dermal LD50 is > 5000 mg/kg.

Reliability: 2

Reference: 10

Identity: Dimethyl Methylphosphonate, Sample N. 540811

Guideline: Federal Hazardous Substances Act Regulations Part 1500

Year: 1981

GLP: Yes

Method: Six albino rabbits received dermal application of 2000 mg/kg dimethyl methylphosphonate to approximately 10% of the body surface. Three of the six application sites were abraded. The application sites were then wrapped for 24 hours. The animals were observed for mortality for 14 days.

Results: There was no mortality in this study. The acute dermal LD50 is > 2000 mg/kg.

Reliability: 1
Reference: 11

5.13 Acute Eye Irritation

Identity: Fyrol DMMP Lot No. 756-79-6
Guideline: U.S. EPA Guidelines for Registering Pesticides, Fed. Reg. 43:163, 37336
Year: 1982
GLP: Yes
Method: Nine albino rabbits received 0.1 ml of Fyrol DMMP in one eye of each rabbit. The other eye acted as a corresponding control. Six of the treated eyes remained unwashed for the duration of the study, while three of the treated eyes were rinsed with water. The animals were observed daily for seven days. The study was terminated on the seventh day because there was no eye irritation. The treated eyes were examined 24, 48, and 72 hours after treatment, and on days 4 and 7. The eye irritation was scored according to Draize
Results: Fyrol DMMP caused mild conjunctival irritation in six unwashed eyes and in one washed eye. This irritation cleared by day 4. The average draize for conjunctival irritation score at 24 and 72 hours, and at 4 days are 3.3, 0.7, and 0.0, respectively. Fyrol DMMP is a mild eye irritant.
Reliability: 1
Reference: 7

Identity: MCTR-129-78
Guideline: Federal Hazardous Substance Labelling Act Section 1500.42
Year: 1978
GLP: No
Method: Six albino rabbits each received 0.1 ml of the test material in one eye. The other eye served as the nontreated control eye. The treated eyes remained unwashed during the 7 day observation period. Ocular reaction to the test substance was graded according to Draize.
Results: MCTR-129-78 caused mild irritation to the conjunctivae, but caused no irritation to the cornea or iris. The test substance is a mild eye irritant.
Reliability: 2
Reference: 12

Identity: Dimethyl Methylphosphonate
Guideline: Federal Hazardous Substance Labeling Act Section 1500.42
Year: 1981
GLP: Yes
Method: Six albino rabbits each received 0.1 ml of the test material in one eye. The other eye served as the nontreated control eye. The treated eyes remained

unwashed during the 72 hour observation period. Ocular reaction to the test substance was graded according to Draize.

Results: There was no irritation to the cornea or iris. Mild irritation to the conjunctiva and minimal chemosis was observed through 24 hours. No irritation was observed beyond 24 hours. DMMP was a very mild eye irritant in this study.

Reliability: 1

Reference: 13

5.14 Skin Irritation

Identity: Fyrol DMMP Lot No. 756-79-6

Guideline: U.S. EPA Guidelines for Registering Pesticides, Fed. Reg. 43:163, 37336

Year: 1982

GLP: Yes

Method: Six albino rabbits received 0.5 ml of Fyrol DMMP applied to a previously shaven area of their skin. The skin at the application sites of the rabbits was abraded prior to the administration of the test substance. The sites were covered for 24 hours, after which they were uncovered and examined for irritation. The sites were scored for irritation according to Draize. The study was terminated after the 72 hour examination of the application sites.

Results: There was no irritation at any of the application sites. Fyrol DMMP was determined to be nonirritating to the skin in this test.

Reliability: 1

Reference: 7

Identity: MCTR-129-78

Guideline: Federal Hazardous Substance Labeling Act Section 1500.41

Year: 1978

GLP: No

Method: Six albino rabbits received 0.5 ml of MCTR-129-78 applied to skin sites where the fur had been previously clipped. Each animal had both abraded and nonabraded application sites. After application, the sites were covered for 24 hours. After removal of the covering, the sites were examined for irritation through 72 hours after treatment. The treatment sites were scored for irritation according to the method of Draize.

Results: Mild irritation was observed at 24 hours by not at 72 hours. The authors concluded that MCTR-129-78 was not a dermal irritant.

Reliability: 2

Reference: 14

Identity: Dimethyl Methylphosphonate, Sample No. 540811

Guideline: Federal Hazardous Substances Act Regulations Part 1500

Year: 1981
GLP: Yes
Method: Six albino rabbits received a dermal application of 0.5 mg of dimethyl methylphosphonate to one abraded and one nonabraded skin site. The application sites were then covered for 24 hours. When unwrapped, the sites were examined at 24 and 72 hours for irritation. If irritation was present, it was scored according to Draize.
Results: Very slight irritation was observed at 24 and 72 hours. Thus the test substance was identified as a slight irritant.
Reliability: 1
Reference: 15

5.15 Acute Inhalation

Identity: Dimethyl Methylphosphonate
Guideline: Not stated
Year: 1974
GLP: No
Method: Five male and five female Sprague-Dawley rats were exposed to a nominal concentration of 26.1 mg/l for one hour, in a positive pressue inhalation chamber. The animals were then observed for 14 days for signs of toxicity and for mortality.
Results: Aside from moderate depressions, the animals did not exhibit signs of toxicity. There was no mortality in this study. The inhalation LC50 in this study is greater than nominal 36.1 mg/l.
Reliability: 3
Reference: 16

Identity: MCTR-196-77
Guideline: Not stated.
Year: 1977
GLP: No
Method: Ten laboratory rats were exposed to a single nominal concentration of 20.27 mg/l for one hour. The animals were observed for clinical signs of toxicity and for mortality. The duration of the observation period is not stated.
Results: Minimal signs of toxicity were observed. There was no mortality in this study. The inhalation LC50 is greater than nominal 20.27 mg/l.
Reliability: 3
Reference: 17

Identity:	MCTR-129-78
Guideline:	U.S. EPA Guideline for Pesticide Hazard Evaluation, Subpart F
Year:	1978
GLP:	Yes
Method:	Five male and 5 female Sprague-Dawley rats were exposed to a single nominal concentration of 20.13 mg/l for one hour. The animals were observed for clinical signs of toxicity and for mortality for 14 days post-exposure.
Results:	Various signs of toxicity were observed, including ataxia, stained face and fur, and piloerection. One female rat died approximately 24 hours after exposure. The acute inhalation LC50 in this study is greater than nominal 20.13 mg/l.
Reliability:	3
Reference:	18

5.2 Repeated Dose Toxicity

Identity:	Dimethyl Methylphosphonate Lot No. 4182-2
Guideline:	Not stated
Year:	1981
GLP:	Yes
Method:	Ten male and ten female Fischer 344 rats received either 0, 250, 500, 1000, 2000, or 4000 mg/kg daily via oral gavage, five days per week, for thirteen weeks. The animals were housed five per cage. The animals were observed for clinical signs and mortality during the in-life phase. All animals were necropsied, at which time tissues and organs were removed from each animal for diagnostic pathology. Apparently no clinical chemistry measurements were made in this study.
Results:	All of the rats in the 4000 mg/kg/day group died during the first week of treatment. In the 2000 mg/kg/day group, 6/10 males and 3/10 females died during the study, suggesting that this dose is significantly above the Maximum Tolerated Dose (MTD). There was only one mortality in the 1000 mg/kg/day group. Minimal clinical signs were reported. Liver weights were elevated in the male and female rats that received 2000 mg/kg/day. Microscopic examination of the tissues revealed possible treatment-related effects in the kidneys, testes, and salivary glands. A health check of the animals showed the test animals has a SDA virus infection, which could have compromised the animals and the test results.
Reliability:	2
Reference:	19

5.3 Genetic Toxicity

5.3.1 In Vitro Gene Mutation

Identity: Fyrol DMMP Lot No. 9114H-17
Guideline: Bacterial Reverse Mutation Test (Ames Test)
Year: 1981
GLP: Yes
Method: Fyrol DMMP was added to five *Salmonella typhimurium* tester strains at doses ranging from 0.62 to 50 ul/plate. The test was conducted in the absence and presence of an Aroclor 1254 or Phenobarbital induced rat and mouse liver metabolic activating system. Positive control chemicals were used to confirm the validity of the test.
Results: Fyrol DMMP did not express mutagenic activity in the Ames *Salmonella* assay in the presence or absence of a metabolic activating system.

Reliability: 1
Reference: 20

Identity: MCTR-196-77, Lot No. 0717601
Guideline: Bacterial Reverse Mutation Test (Ames Test)
Year: 1977
GLP: No
Method: MCTR-196-77 was added to five *Salmonella typhimurium* tester strains at doses ranging from 0.001 to 5 ul/plate. The test was conducted in the absence and presence of an Aroclor 1254 induced rat liver metabolic activating system. Positive control chemicals were used to confirm the validity of the test.
Results: MCTR-196-77 was mutagenic in two *Salmonella* strains, TA-1538 and TA-98, in the presence of a metabolic activating system.
[These positive results were superceded in Ref. 18 as result of lab review. Due to a technician error, MCTR-196-77 was retested.]
Reliability: 2
Reference: 21

Identity: MCTR-196-77, Lot No. 0717601
Guideline: Bacterial Reverse Mutation Test (Ames Test)
Year: 1978
GLP: No
Method: The testing facility concluded that the results cited in Ref. 17 were in error probably due to an incorrect addition of chemical to the test by a technician. The data, when carefully reviewed, indicated that the positive control chemicals was probably added to the plates of TA-1538 and TA-98 rather than the test compound. MCTR-196-77 was retested with *Salmonella* strain TA98 at doses ranging from 0.001 to 5 ul/plate. The test

was conducted in the presence of an Aroclor 1254 induced rat liver metabolic activating system. Only TA98 was retested as more sensitive than TA-1538.

Results: As TA-98 did not demonstrate mutagenic activity, it was concluded that MCTR-196-77 did not demonstrate mutagenic activity in any of the assays in the evaluation in the presence or absence of a metabolic activating system. This conclusion supercedes the earlier conclusion in the August 1977 report (Ref. 17).

Reliability: 2

Reference: 22

Identity: MCTR-196-77, Lot. No. 0717601

Guideline: Bacterial Reverse Mutation Test (Ames Test)

Year: 1977

GLP: No

Method: MCTR-196-77 was added to five *Salmonella typhimurium* tester strains at five doses, which differed per tester strain. The test was conducted in the absence and presence of an Aroclor 1254 induced rat liver metabolic activating system. Positive control chemicals were used to confirm the validity of the test.

Results: MCTR-196-77 did not demonstrate mutagenic activity in any of the five tester strains in the presence or absence of a metabolic activating system.

Reliability: 2

Reference: 23

Identity: MCTR-129-78, VGC 89549

Guideline: Bacterial Reverse Mutation Test (Ames Test)

Year: 1978

GLP: No

Method: MCTR-129-78 was added to five *Salmonella typhimurium* tester strains at doses ranging from 0.01 to 10 ul/plate. The test was conducted in the absence and presence of an Aroclor 1254 induced rat liver metabolic activating system. Positive control chemicals were used to confirm the validity of the test.

Results: MCTR-129-78 did not demonstrate mutagenic activity in any of the five tester strains in the presence or absence of a metabolic activating system.

Reliability: 2

Reference: 24

Identity: Fyrol DMMP Lot No. 9114H-17

Guideline: In Vitro Mammalian Cell Gene Mutation Test

Year: 1981

GLP: Yes

Method: Fyrol DMMP was added to L5178Y mouse lymphoma cell cultures at ten

different doses. Positive control chemicals were added to other mouse lymphoma cells to confirm the validity of the assay. Fyrol DMMP was tested in the absence and presence of a rat liver metabolic activating system.

Results: In the absence of an activating system, Fyrol DMMP demonstrated mutagenic activity in a dose-related manner, with significant mutation frequency at 35 ul/ml. In the presence of a rat liver metabolic activating system, Fyrol DMMP expressed mutagenic activity at all dose levels above 5.0 ul/ml. Fyrol DMMP demonstrated mutagenic activity, in the form of gene mutation, in the absence and presence of an activating system, in the L5178Y mouse lymphoma mammalian cell assay.

Reliability: 1

Reference: 25

Identity: Dimethyl Methylphosphonate, Sample No. 540811

Guideline: In Vitro Mammalian Cell Gene Mutation Test

Year: 1981

GLP: Yes

Method: Dimethyl methylphosphonate was evaluated in the L5178Y mouse lymphoma cell assay at doses ranging from 7.5 ul/ml to 42.2 ul/ml, with and without an Aroclor-induced rat liver metabolic activating system. Appropriate positive control chemicals were included in the assay to assure validity.

Results: Dimethyl methylphosphonate demonstrated a dose-related increase in mutatation frequency with increasing doses, in both the activated and nonactivated mammalian cell systems.

Reliability: 1

Reference: 26

5.3.2 In Vitro Chromosome Aberrations

Identity: Fyrol DMMP Lot No. 9114H-17

Guideline: In Vitro Mammalian Chromosomal Aberration Test

Year: 1982

GLP: Yes

Method: Fyrol DMMP was added to L5178 mouse lymphoma cells at doses ranging from 5.0 ul/ml to 45 ul/ml, in the presence and absence of an Aroclor 1254 rat liver metabolic activating system. Positive control chemicals were added to L5178 cell to confirm the validity of the assay. After exposure to the test substance, the cells were evaluated for chromosomal aberrations and sister chromatid exchanges.

Results: Fyrol DMMP induced a significant increase in various types of chromosomal aberrations and sister chromatid exchanges in the presence and absence of a metabolic activating system. These increases in mutagenic activity occurred in a dose-related manner.

Reliability: 1
Reference: 27

5.3.3 In Vivo Mutagenicity Tests

Identity: Fyrol DMMP Lot No. 1114L-6-1
Guideline: Sex-linked Recessive Lethal Test in Drosophila Melanogaster
Year: 1982
GLP: Yes
Method: Fyrol DMMP was fed to adult male fruit flies (*Drosophila melanogaster*) at one of two dose levels. Additional male flies were included in negative and positive control groups. The treated and negative control males were then mated with nontreated females. The offspring were examined to determine the incidence of sex-linked recessive lethal mutations.
Results: Fyrol DMMP did not induce sex-linked recessive lethal mutations, as there was no increase in the frequency of mutations except in the positive control flies. Fyrol DMMP did not demonstrate mutagenic activity in this assay.
Reliability: 1
Reference: 28

Identity: Fyrol DMMP Lot No. 9114H-17
Guideline: Mammalian Bone Marrow Chromosomal Aberration Test
Year: 1982
GLP: Yes
Method: Male Sprague-Dawley rats received either a single dose or five consecutive doses of Fyrol DMMP, at dose levels from 556 to 5000 mg/kg/day. Three hours prior to sacrifice, the animals received an intraperitoneal injection of colchicine to arrest the cells in metaphase. Animals were sacrificed either 6, 12, 24, or 48 hours after dosing. Bone marrow cells were collected from the tibia and/or femur, processed and placed on slides, and the cells were examined for structural changes to the chromosomes, and rearrangements of chromosomes. Positive and negative groups were included in the study.
Results: There was no increase in the frequency of chromosomal aberrations or rearrangements in the treated animals when compared to the negative control group. The positive control, cyclophosphamide, induced a significant increase in chromosomal aberrations. Fyrol DMMP was not mutagenic in this assay.
Reliability: 1
Reference: 29

5.3.4 In Vitro Mammalian Cell Transformation

Identity: Fyrol DMMP Lot No. 9114H-17

Guideline: Not stated.
Year: 1983
GLP: Yes
Method: To determine whether Fyrol DMMP is able to transform cultures of normal BALB/3T3 cells, the cells were exposed to the test material at doses ranging from 0.625 ul/ml to 10 ul/ml, for about 5 weeks. The flasks were then examined for transformed foci.
Results: A dose-dependent increase in the number of transformed foci was observed. Although this increase did not exceed 1.7 times the control (background transformation) values, it was statistically significant and indicates that Fyrol DMMP has weak mammalian cell transforming activity.
Reliability: 1
Reference: 30

5.4 Carcinogenicity

Identity: Fyrol DMMP Lot No. 11146L-6 and 1114L-2-1
Guideline: National Toxicology Program Carcinogenicity Bioassay
Year: 1987
GLP: Yes
Method: Groups of 50 male and 50 female Fischer 344 rats received either 0, 500, or 1000 mg/kg dimethyl methylphosphonate (DMMP) in corn oil via gavage, five days per week for 103 weeks. Groups of 50 male and 50 female B6C3F1 mice received either 0, 1000, or 2000 mg/kg, five days per week for 102 weeks. The animals were housed five per cage. All animals were observed twice daily. Animals found moribund were humanely terminated and examined via necropsy. At the conclusion of the study, all animals were examined during necropsy and specified tissues were removed, weighed, and placed in formalin for diagnostic pathology. All specified tissues were subsequently evaluated by microscopic examination.
Results: Near the end of the in-life phase, the body weights of the high dose male and female rats were significantly lower than the body weights of the corresponding control animals. No DMMP-related clinical signs were reported in the treated rats. Survival of male rats in all groups was greater than 50% until week 80, after which survival decreased to 27/50 in control group, 17/50 in low dose group, and 4/50 in the high dose males. Survival of the high dose female rats also decreased, but not as substantially as in the males. DMMP treatment resulted in nephropathy of the collecting tubules of the kidneys in the male rats (12/50 controls, 41/50 low dose, 36/49 high dose), focal hyperplasia in the male rat renal tubules (0/50, 8/50, 9/49), and the occurrence of renal tubular cell adenocarcinoma (0/50, 2/50, 3/49). There were no renal tubule alterations in the female

rats. The NTP concluded that there was some evidence of carcinogenic activity in the male rats based on the occurrence of the renal tubule adenocarcinomas. The NTP did not equate the formation of the renal tumors to the presence of hyaline droplets present in the renal tubule epithelial cells, reported by the study pathologist, even though it is well recognized that a male rat specific mechanism has been identified that correlates the presence of the hyaline droplets with the induction of alpha-2u-globulin and the subsequent induction of renal tumors. The lack of renal tumors in the female rats supports the alpha-2u-globulin mechanism which is specific to the male rat.

Survival at the end of the study in male mice was 29/50 in vehicle control, 12/50 in the low dose and 0/50 in the high dose, and in female mice, 41/50, 30/50, and 2/50, respectively. While the NTP reports the mouse segment as "an inadequate study of carcinogenic activity because of decreased survival," it is important to note that even though the high dose was clearly above the Maximum Tolerated Dose, DMMP did not induce a significant incidence of tumors in any tissue in either male or female mice.

Reliability: 1
Reference: 31

5.5 Reproductive Toxicity

Identity: Fyrol DMMP Lot No. 11146L-6 and 1114L-2-1
Guideline: National Toxicology Program Special Study
Year: 1984
GLP: Yes
Method: Five groups of 20 male Fischer 344 rats received 0, 250, 500, 1000, or 2000 mg/kg of DMMP, via gavage, five days per week for ninety days. They were then mated with untreated female Fischer 344 rats. Endpoints measured include sperm count and motility, mating index, number of resorptions, LH and FSH levels, and the histopathology of the male reproductive organs.
Results: There was a dose-related decrease in sperm count, sperm motility, and mating index. The male fertility index was 70, 75, 60, 40, and 0 in the 0, 250, 500, 1000, and 2000 mg/kg groups, respectively. DMMP expressed activity as a dominant lethal mutagen by increasing the number of early resorptions with increasing dose (control 6.1% vs 14.9, 37.8, and 79.1%). Microscopic examination of the testes revealed histologic abnormalities only in the high dose group. These changes included decreased spermatogenesis and degenerative lesions.
Reliability: 1
Reference: 32

Identity:	Fyrol DMMP Lot No. 11146L-6 and 1114L-2-1
Guideline:	National Toxicology Program Special Study
Year:	1984
GLP:	No
Method:	Male Fischer 344 rats received 1750 mg/kg DMMP via oral gavage daily for up to 12 weeks. Reproductive tissues were collected and processed for examination by light microscopy. A reversibility phase was included in the study.
Results:	Daily oral treatment with DMMP resulted in changes to spermatogenesis and to the seminiferous tubule morphology. A significant alteration of sperm maturation and spermiation was observed, with degenerative lesions in the tubules. After a 14 week recovery period, the treated animals showed significant but incomplete reversal of the DMMP effects. DMMP did not adversely affect the epididymis.
Reliability:	2
Reference:	33

Identity:	Fyrol DMMP Lot No. 11146L-6
Guideline:	National Toxicology Program Special Study
Year:	1984
GLP:	No
Method:	Groups of male B6C3F1 mice were treated with either 0, 250, 500, 1000, or 2000 mg/kg DMMP by gavage, five days per week for 13 weeks. The treated males were mated with untreated female mice.
Results:	The two highest doses resulted in an increase in early resorptions, which suggests a dominant lethal effect. After a 15 week recovery period, there were no remaining adverse effects. Male mice are less responsive than the male rat to the reproductive toxicity of DMMP.
Reliability:	2
Reference:	34

5.6 *Developmental Toxicity (Teratogenicity)*

Identity:	Dimethyl Methylphosphonate
Guideline:	EPA Subdivision F Section 83-3
Year:	1978
GLP:	No
Method:	Groups consisting of 25 pregnant Sprague-Dawley rats each received either CMC (vehicle) or DMMP at 100, 1000, or 2000 mg/kg/day via oral gavage from gestation day 6 through day 15. The pregnant animals were sacrificed on gestation day 21 and the fetuses were removed, weighed, sexed, and examined microscopically for malformations (developmental anomalies).
Results:	The high dose, 2000 mg/kg/day, caused maternal toxicity which was

	expressed as decreased body weight gain and decreased food consumption. Although an examination of the fetuses from this group showed fetotoxicity, seen as lower body weights and delayed skeletal development, there was no increase in the incidence of fetal malformations. Dimethyl methylphosphonate did not demonstrate teratogenic activity in this study.
Reliability:	2
Reference:	35

Identity:	Dimethyl Methylphosphonate
Guideline:	Special Study
Year:	1987
GLP:	No
Method:	Fifty pregnant CD-1 mice were administered 4175 mg/kg/day DMMP by oral gavage on gestational days 6 through 13. The mice were allowed to deliver their offspring.
Results:	An examination of the offspring revealed reduced body weights but no adverse effect on litter size, viability, or organ development.
Reliability:	4
Reference:	36

References

1. Material Safety Data Sheet, Akzo Nobel Functional Chemicals, January 29, 2003.
2. Akzo Nobel Functional Chemicals LLC, Vapor Pressure Data by Isoteniscope. June 2000. Akzo Nobel internal report (unpublished report).
3. Akzo Nobel Functional Chemicals LLC, Water Solubility and Partition Coefficient of Dimethyl Methylphosphonate. October 29, 2001. Akzo Nobel internal report (unpublished report).
4. Krikorian, S.E. et al., Determination of the Partition Coefficients of Organophosphorus Compounds Using High Performance Liquid Chromatography. Government Report Announcements, Issue 12, 1988.
5. Life Science Research Limited, Fyrol DMMP: Activated Sludge – Respiration Inhibition Test, Study No. 89/AKL025/1064, 1990, Akzo Nobel internal report (unpublished report).
6. Life Science Research Limited, Fyrol DMMP: Acute Toxicity to Rainbow Trout, Study No. 90/0162, 1990, Akzo Nobel internal report (unpublished report).
7. Stauffer Chemical Company, Study No. T-10594, Acute Toxicity of Fyrol DMMP in Rats. June 16, 1982, Akzo Nobel internal report (unpublished report).
8. Mobil Environmental and Health Science Laboratory, The Acute Oral Toxicity of Dimethyl Methylphosphonate in Albino Rats. Study No. 546-81, June 18, 1981, Rhodia internal report (unpublished report).
9. Cannon Laboratories, Inc. Study No. 7E-7020. Report on the Acute Dermal Toxicity of Rabbits (MCTR-196-77). August 24, 1977, Company report number M1961-77, Rhodia internal report (unpublished report).
10. Cannon Laboratories, Inc. Study No. 8E-2384. Report on the Acute Dermal Toxicity of Rabbits (MCTR-129-78). August 21, 1978, Company report number M1293-78, Rhodia internal report (unpublished report).
11. Mobil Environmental and Health Science Laboratory, The Acute Dermal Toxicity of Dimethyl Methylphosphonate in Rabbits. Study No. 545-81, June 18, 1981, Rhodia internal report (unpublished report).
12. Cannon Laboratories, Inc. Study No. 8E-2381. Report on Rabbit Eye irritation (MCTR-129-78). August 11, 1978, Company report number M1295-78, Rhodia internal report (unpublished report).
13. Mobil Environmental and Health Science Laboratory, Primary Eye Irritation of Dimethyl Methylphosphonate. Study No. 644-81. June 26, 1981. Rhodia internal report (unpublished report).
14. Cannon Laboratories, Inc. Study No. 8E-2382. Report on Primary Dermal Irritation in Rabbits (MCTR-129-78). August 8, 1978, Company report number M1296-78, Rhodia internal report (unpublished report).
15. Mobil Environmental and Health Science Laboratory, Skin Irritation of Dimethyl Methylphosphonate After a Single Application to Albino Rabbits. Study No. 543-81. June 26, 1981, Rhodia internal report (unpublished report).
16. Stauffer Chemical Company, Study No. T-4551. Acute Inhalation Toxicity. February 27, 1974, Akzo Nobel internal report (unpublished report).
17. Cannon Laboratories, Inc., Study No. 7E-7021. Acute Inhalation Toxicity (MCTR-196-77). July 7, 1977, Company report number M1962-77, Rhodia internal report (unpublished report).

18. Cannon Laboratories, Inc. Study No. 8E-2385. Acute Inhalation Toxicity Study of MCTR-129-78. August 30, 1978. Company report number M1293-78. Rhodia internal report (unpublished report).
19. Litton Bionetics, Inc. Subchronic Study (13-Week) in Rats – Dimethyl Methylphosphonate. February 1981, Akzo Nobel internal report (unpublished report).
20. Stauffer Chemical Company, Study No. T-10498. Mutagenicity Evaluation in Salmonella typhimurium. April 8, 1981, Akzo Nobel internal report (unpublished report).
21. Litton Bionetics, Inc. Study No. 2683. Mutagenicity Evaluation of MCTR-196-77. August 18, 1977, Company report number M1963-77, Rhodia internal report (unpublished report).
22. Litton Bionetics, Inc. Study No. 2683. Update: Mutagenicity Evaluation of MCTR-196-77. January 18, 1977, Company report number M1964-77, Rhodia internal report (unpublished report).
23. Microbiological Associates, Study No. T1170. Activity of MCTR-196-77 in the *Salmonella*/Microsomal Assay for Bacterial Mutagenicity. October 5, 1977, Company report number M1965-77, Rhodia internal report (unpublished report).
24. Litton Bionetics, Inc. Study No. 3396. Mutagenicity Evaluation of MCTR-129-78 in the Ames *Salmonella*/Microsome Plate Test. August 16, 1978, Company report number M1291-78, Rhodia internal report (unpublished report).
25. Stauffer Chemical Company, Study No. T-10499. Mutagenicity Evaluation in Mouse Lymphoma Forward Mutation Assay. April 8, 1981, Akzo Nobel internal report (unpublished report).
26. Mobil Environmental and Health Science Laboratory, Study No. 542-81. A Murine Lymphoma Mutagenesis Assay, Heterozygous at the Thymidine Kinase Locus for the Determination of the Potential Mutagenicity of Dimethyl Methylphosphonate. July 21, 1981, Rhodia internal report (unpublished report).
27. Stauffer Chemical Company. Study No. T-10499. Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test – Cytogenetic Assay. January 13, 1982, Akzo Nobel internal report (unpublished report).
28. Litton Bionetics, Inc. Mutagenicity Evaluation of Fyrol DMMP in the Sex-Linked Recessive Lethal Test in Drosophila Melanogaster. Study No. 22161. September 15, 1982, Akzo Nobel internal report (unpublished report).
29. Stauffer Chemical Company. Study No. T-10885. Mutagenicity Evaluation in Bone Marrow Cytogenetic Analysis in Rats. December 22, 1982, Akzo Nobel internal report (unpublished report).
30. Stauffer Chemical Company. Study No. T-10500. Morphological Transformation of BALB/3T3 Cells. March 16, 1983, Akzo Nobel internal report (unpublished report).
31. National Toxicology Program. Toxicology and Carcinogenesis Studies of Dimethyl Methylphosphonate in Fischer 344 Rat and B6C3F1 Mice. November, 1987.
32. Dunnick, J.K. et al., Reproductive Toxicity of Dimethyl Methylphosphonate in the Male Fischer 344 Rat. Toxicol. Appl. Pharmacol. 72:379-387, 1984.
33. Chapin, R.E. et al., Development of Reproductive Tract Lesions in Male Fischer 344 Rats After Treatment with Dimethyl Methylphosphonate. Exp. Mol. Pathol. 41:126-140, 1984.
34. Dunnick, J.K. et al., Dimethyl Methylphosphonate Induction of Dominant Lethal Mutations in Male Mice. Mutat. Res. 138:213-218, 1984.
35. Ciba-Geigy Ltd. Study No. FAT80-021. Test for Teratogenic or Embryotoxic Effects. TSCA Submission. EPA Document No. OTS-0784-0242-2. 1978.

36. Hardin, B.D. et al., Evaluation of 60 Chemicals in a Preliminary Developmental Toxicity Test. Journal of Teratogenicity, Carcinogenicity, and Mutagenicity 7:29-48, 1987.